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EFFECTIVENESS OF ORGANOPHOSPHORUS COMPLEXONS IN INTRATRACHEAL POISONING WITH BERYLLIUM CHLORIDE

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EFFECTIVENESS OF ORGANOPHOSPHORUS COMPLEXONS IN INTRATRACHEAL POISONING WITH BERYLLIUM CHLORIDE

[Effektivnost' fosfororganicheskikh kompleksonov pri intratrakheal'nom otravlenii khloristym berilliyem]

by

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Experiments conducted on 340 mice and 170 rats gave evidence that the organophosphorus complexon DTPP (calcium-sodium salt of diethylenetriaminepentamethylphosphonic acid), by single intraperitoneal administration, greatly mitigates pulmonary edema, provoked by intratracheal administration of beryllium chloride, and it increases survival of the animals. Radioisotope investigations demonstrated that DTPP contributes to more rapid elimination of the beryllium ion from the body, in cases of intratracheal poisoning with beryllium chloride.

Soluble beryllium compounds are so highly toxic and dangerous, that acute inhalation poisoning can arise by inhalation of a total of 0.55-4 mg of the salt in the course of a day (Eisenbud and colleagues, 1948; Stokinger and colleagues, 1950). This kind of acute intoxication occurs, with primary affliction of the respiratory passages, and it is manifested in a number of cases by acute pulmonary edema with an unfavorable

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outcome (A. Ye. Vermel', 1961; Tepper and colleagues, 1961, and others). L. G. Arkhipova and colleagues (1964, 1965, 1967, 1968) determined that phosphorus analogs of polyaminopolyacetic acids have a high selectivity for the beryllium ion, forming stable, water-soluble complexes with it, which facilitate elimination of this metal from the body and prevent the death of the animals, by intraperitoneal administration of absolutely lethal doses of soluble beryllium salts.

The purpose of this work is to investigate the therapeutic effect of organophosphorus complexons in toxic pulmonary edema, caused by beryllium chloride, as well as the study of the ability of these preparations to accelerate elimination of beryllium from the body, in intratracheal poisoning.

Methods of Investigation

The work was conducted on 340 female white mice, weighing 24-25 g, and on 170 female white rats, weighing 180-200 g. In the tests on rats, the amount of beryllium chloride water solution introduced into the trachea was 0.15 ml per 100 g of weight and, in the test on mice, 0.03 ml per 10 g of weight. Intratracheal inoculation was accomplished bloodlessly under ether Rausch narcosis with visual control.

The disodium salt of ethylenediamine-bis-isopropyl phosphonic acid (phosphicine) and the calcium-sodium salt of diethylenetriaminepentamethylphosphonic acid (DTPP) were administered intraperitoneally 10-15 min after intratracheal poisoning.

The effectiveness of the complexons was evaluated by survival of the animals in the acute phase of intoxication and the intensity of pulmonary edema. Besides, the effect of DTPP on beryllium content in the

body was studied, by the radioisotope method. For this, Be^7Cl_2 (5 μ curie per rat) was administered intratracheally, together with stable beryllium chloride, at a dose of 1 mg/kg (maximum tolerable dose). The Be^7 content in the organs was evaluated by measurement of the γ-radiation, using a γ scintillation sensor with NaI(Cs) crystal and a PP-8 radiometer. The investigation was carried out by comparison with a standard.

Results and Discussion

Acute intratracheal poisoning with beryllium chloride occurred with manifestation of toxic pulmonary edema. Death of the rats began on the first day after administration of the preparation, and the mice died on the second/third day. Upon autopsy, hyperemia and considerable pulmonary edema were observed macroscopically, and large amounts of a foamy fluid escaped from the trachea and bronchi. The pulmonary coefficient was doubled or tripled. In intact rats, the index of dry lung residue was 21.08±0.85 and, 6 hours after poisoning, 11.28±0.29, which is evidence of development of a true pulmonary edema, in distinction from plethora, in which the dry lung residue is almost unchanged.

Phosphicine hardly increased survival of the animals, despite some reduction in pulmonary edema (Table I).

The DTPP complexon proved to be effective in the dose range from 100 to 500 mg/kg: It tripled survival of the animals in the acute phase of intoxication, and it cut the intensity of pulmonary edema almost in half (see Table I). Moreover, a single intraperitoneal administration of DTPP (500 mg/kg), 10-15 min after intratracheal poisoning with beryllium chloride reduced the beryllium content in the organs of treated rats by the seventh day, compared with that in the untreated ones: By 1.36 times

TABLE I

Effect of organophosphorus complexons on outcome of intratracheal intoxication with beryllium chloride

a Доза хлористого бериллия (в мг/кг)	b Препарат	c Доза (в мг/кг)	d Легочный коэффициент	e Число животных: f всего	e Число животных: g из них выжило	h % выживаемости к 7-м суткам
	i Белые мыши					
—	j Интактные		7,7±0,2	—	—	—
4	k Без лечения		23,5±1,7	60	15	25
4	l Фосфицин	500	15,6±0,8	20	5	25
4	m ДТПФ	500	12,2±0,6	40	26	65
4	ДТПФ	400	—	20	14	70
4	ДТПФ	300	—	20	12	60
4	ДТПФ	200	13,6±0,6	60	42	70
4	ДТПФ	100	—	60	41	68
4	ДТПФ	50	—	20	4	20
	n Белые крысы					
5	k Без лечения		—	40	9	22,5
5	l Фосфицин	500	—	26	9	34,6
5	m ДТПФ	250	—	40	25	62,5

Key:
a Beryllium chloride dose (in mg/kg)
b Preparation
c Dose (in mg/kg)
d Pulmonary coefficient
e Number of animals
f Total
g Surviving
h % 7-day survival
i White mice
j Intact
k Untreated
l Phosphicine
m DTPP
n White rats

[Translator's Note: Commas in tabulated figures in Tables I and II are equivalent to decimal points.]

in the lungs, 2 times in the liver, 1.77 times in the kidneys and more than 2 times in the bones (Table II). The total beryllium content in the body decreased 1.5 times.

Repeated use of the complexon, 10 min and 6 hours after intratracheal poisoning, did not increase elimination of beryllium over that in the single administration.

Thus, the polyaminopolyphosphonic complexon DTPP considerably reduces pulmonary edema, upon entry of beryllium chloride into the respiratory passages, facilitates more rapid elimination of the toxic ion from the body and increases survival of the animals.

It should be noted at the same time that the effectiveness of the complexon, in intratracheal poisoning with beryllium chloride, is less

TABLE II

Effect of calcium-sodium salt of diethylenetriaminepentamethylphosphonic acid on beryllium content (in % of amount introduced) in the organs of rats with acute intratracheal poisoning (M±m)

a Срок исследования	d Легкие		e Печень		f Почки
	b контроль	c опыт	b контроль	c опыт	b контроль
6-й час j	66,14±11,09	56,27±11,82	0,97±0,42	0,61±0,36	0,27±0,09
1-е сутки k	60,87±7,62	44,46±9,26	1,98±0,71	0,60±0,29	0,42±0,15
3-и сутки l	46,00±8,17	38,90±9,16	2,95±0,45	1,97±0,77	0,57±0,14
7-е сутки m	40,47±5,61	29,67±6,58	3,53±0,59	1,80±0,62	0,48±0,13

i *Продолжение*

a Срок исследования	f Почки	g Кости		h Общее содержание	
	c опыт	b контроль	c опыт	b контроль	c опыт
6-й час j	0,17±0,07	2,31±1,34	2,00±0,59	79,79±7,92	66,25±8,18
1-е сутки k	0,25±0,09	4,98±1,81	3,00±1,61	74,24±7,19	56,32±9,63
3-и сутки l	0,41±0,15	10,02±3,16	5,50±1,75	60,31±10,12	48,30±8,37
7-е сутки m	0,27±0,07	13,17±3,48	6,12±1,89	58,35±7,18	38,44±6,67

Key:
- a Time of examination
- b Control
- c Test
- d Lungs
- e Liver
- f Kidneys
- g Bones
- h Total content
- i Continued
- j 6th hour
- k 1st day
- l 3rd day
- m 7th day

pronounced than in intraperitoneal, which most likely is connected with development of toxic pulmonary edema upon entrance of beryllium into the respiratory passages. Besides, intraperitoneal administration of beryllium and the complexon creates optimum conditions for inactivation of the metal ion in situ.

It is likely that, in intratracheal poisoning with soluble beryllium salts, the therapeutic effect of DTPP can be strengthened by using antiedema agents. Moreover, further search is necessary for conditions and preparations which weaken the bonding of beryllium to high molecular weight biocomplexes of the body and which assist in the reaction of the complexons with the incorporated metal.

Conclusions

1. Beryllium chloride causes acute toxic pulmonary edema by intratracheal entry.

2. The polyaminopolyphosphonic complexon (DTPP), being an agent of etiological therapy, accelerates elimination of beryllium from the body, reduces pulmonary edema and increases survival of animals in cases of intratracheal poisoning with beryllium chloride.

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